



# Outcomes Assessment

## Increased Risk of Adverse Drug Events in Pediatric Patients on Antidepressant Therapy

Prepared for Kansas Medical Assistance Program in March, 2005

### EXECUTIVE SUMMARY

**Purpose of Intervention** The intervention is intended to advise physicians of the FDA recommended boxed warnings on all antidepressants and foster ongoing evaluation and monitoring of antidepressant therapy in their pediatric patients.

Intervention	Intervention Type	Population-based mailing
	Intervention Mailing Date	June 2004
	Pre-intervention Period (Baseline)	January 2004 – June 2004
	Post-intervention Period (Post)	August 2004 to January 2005
	Number of Letters Mailed	449
	Number of Targeted Physicians	449
	Number of Targeted Patients	1,683
	Adjusted Targeted Patients	1,238
	Number of Control Physicians	0
	Number of Control Patients	0
	Adjusted Control Patients	0

### Changes in Clinical Indicators

Clinical Indicators	Target		
	Baseline	Jul-04	% Change
Increased Risk of ADE	1,238	800	-35.4%

### Savings Calculations

Intervention-Related Drug Therapy	
Targeted Group: Actual Average Paid Amount Per Patient Per Month (Baseline)	\$62.77
Targeted Group: Actual Average Paid Amount Per Patient Per Month (Post)	\$54.06
Estimated Savings Per Patient Per Month	\$8.71
Total Number of Targeted Patients	1,238
6-Month Total Savings	\$64,701.08



## BACKGROUND

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As reported by Reuters, based on pharmacy claims data, the number of children and teenagers taking antidepressants has fallen more than 20% this year after warnings and concerns that these drugs may increase suicidal tendencies.<sup>1</sup> This outcome comes after over a year of investigation by the Food and Drug Administration (FDA) and after the agency's recommendation for the manufacturers of ten antidepressants to include stronger warnings.

Recent investigations have determined that two to three out of every 100 young people treated with antidepressants may face an elevated risk of suicidal thoughts or actions.<sup>2</sup> On September 14, 2004, an advisory panel to the FDA voted 15-8 to urge the agency to require a black-box warning on antidepressants, to get the message to physicians. Some panelists said they felt the drugs were over-prescribed and they hoped use would decline. Studies have failed to show that most of the antidepressant drugs work in children, something the panel said should be highlighted on the drug labels. Only fluoxetine (Prozac) has been shown to work in children and is FDA-approved for pediatric use. The FDA is not bound to follow recommendations from the advisory panel, but frequently does.<sup>3</sup>

Additionally, the FDA acknowledged the increase in suicidal tendencies was not a result of the children's underlying depression but was caused by the medications themselves.<sup>3</sup> The FDA analysis showed the relative risks of suicidal behavior were highest among youths taking fluvoxamine (Luvox), venlafaxine (Effexor), paroxetine (Paxil), and were lower in youths taking citalopram (Celexa), sertraline (Zoloft), and fluoxetine (Prozac).<sup>4</sup>

On September 16, 2004, the FDA issued a statement that the agency generally supports the recommendations made to the agency by both advisory committees.<sup>5</sup> The statement acknowledged that the FDA is working to adopt new labeling to enhance the warnings associated with use of antidepressants and to bolster information provided to patients when these drugs are dispensed. Other important information was supplied in the FDA statement. The members of the advisory committees:

- endorsed FDA's approach to classifying and analyzing the suicidal events and behaviors observed in controlled clinical trials and expressed their view that the new analyses increased their confidence in the results;
- concluded that the finding of an increased risk of suicidality in pediatric patients applied to all the drugs studied (fluoxetine (Prozac), sertraline (Zoloft), mirtazapine (Remeron), paroxetine (Paxil), venlafaxine (Effexor), citalopram (Celexa), bupropion (Wellbutrin), fluvoxamine (Luvox) and nefazodone (Serzone)) in controlled clinical trials;
- recommended that any warning related to an increased risk of suicidality in pediatric patients should be applied to all antidepressant drugs, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single medication from an increased risk;

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<sup>1</sup> Youth Antidepressant Use Down Due to Risks-Medco. September 21, 2004. Reuters news article. Available at: [www.reuters.com](http://www.reuters.com). Accessed September 21, 2004.

<sup>2</sup> US FDA agrees on antidepressant risks for youth. September 16, 2004. Reuters news article. Available at: [www.reuters.com](http://www.reuters.com). Accessed September 16, 2004.

<sup>3</sup> Vedantam S. FDA confirms antidepressants raise children's suicide risk. Washington Post, Tuesday, September 14, 2004, Page A01. Also available at: [www.washingtonpost.com](http://www.washingtonpost.com).

<sup>4</sup> Henderson D. Feds warn on children and antidepressants. Associated Press, Tuesday, September 14, 2004. Available at: [www.story.news.yahoo.com](http://www.story.news.yahoo.com).

<sup>5</sup> FDA Statement. FDA statement on recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees. September 16, 2004. Available at: [www.fda.gov](http://www.fda.gov). Accessed September 16, 2004.



- reached a split decision (15-yes, 8-no) regarding recommending a "black-box" warning related to an increased risk for suicidality in pediatric patients for all antidepressant drugs;
- endorsed a patient information sheet ("Medication Guide") for this class of drugs to be provided to the patient or their caregiver with every prescription;
- recommended that the products not be contraindicated in this country because the Committees thought access to these therapies was important for those who could benefit; and
- recommended that the results of controlled pediatric trials of depression be included in the labeling for antidepressant drugs.

On October 15, 2004, the FDA directed manufacturers of all antidepressant drugs to revise the labeling for their products to include a boxed warning as well as expanded warning statements. These statements will alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with antidepressants, and to include additional information about the results of pediatric studies.

The FDA has determined that the following points are appropriate for inclusion in the boxed warning:<sup>6</sup>

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).

The FDA also recommends that pediatric patients being treated with antidepressants *for any indication* be closely observed for clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behavior. Observation for these changes is especially important during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This monitoring should include daily observation by families and caregivers and frequent contact with the physician. Additionally, the FDA also recommends that prescriptions for antidepressants be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.<sup>6</sup>

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<sup>6</sup> FDA Public Health Advisory October 15, 2004. Available at <http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm>



## METHODOLOGY

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Changes in intervention-related pharmacy dollars paid, pharmacy dollars paid per patient per month (PPPM), number of pharmacy claims, and intervention-related drug utilization were examined. This intervention identified providers whose patients were affected by increased risk of adverse drug events. To assess the impact of the intervention, pharmacy drug claims were reviewed from August 2004 through January 2005.

Clinical Criteria: Criteria, rationale, and text message(s) to providers are listed below. All physicians with at least one recipient “hitting” on criteria received letters.

- Increased Risk of Adverse Drug Events

The increased risk of adverse drug event indicator identifies patients receiving medications who are at risk of experiencing an adverse drug event due to predisposing medical conditions. Additionally, certain concomitant medication therapy may result in additive effects resulting in adverse events.

Rationale: Medication related adverse events are common in primary care, and many are preventable or ameliorable. Improvements in monitoring for and responding to symptoms are especially important for the prevention of adverse drug events in outpatients.

Sample Provider Paragraph:

According to submitted pharmacy and medical claims data it appears your pediatric patient is receiving fluoxetine, fluvoxamine or sertraline for the treatment of obsessive compulsive disorder. For patients receiving antidepressants, the FDA recommends close observation for worsening of depression or suicidality, whether or not the patient initially presented with depressive symptoms. Patients whose conditions are stable and exhibit no signs of suicidal thoughts or worsening depression should continue to be routinely monitored, especially when starting a new drug regimen, and during dose changes.

Definitions:

**Adjusted Target Patients** – All patients of physicians who were included in the intervention, who had pharmacy claims and were active plan members throughout the post-intervention time period. Additionally, when outcomes are performed, these patients’ pre-intervention (baseline) hits are re-evaluated to make certain that the status of clinical indicators haven’t changed for each patient due to late pharmacy and medical claims.

**Intervention-Related Drugs** – Antidepressant medications.

## RESULTS

### Characteristics

Table 1 describes the patient population included in the population-based intervention based upon mean age, gender, number of providers, average number of prescriptions per patient per month, and utilization of intervention-related drugs at baseline. As can be seen from the table, the target group had fewer females than males, were seeing 3.0 providers, receiving 3.5 prescriptions per month, and taking an average of 1.4 intervention-related drugs.

**Table 1: Patient Characteristics**

	Target (N=1,238)
Mean Age	13.3
Percentage Male	53.6%
Percentage Female	46.4%
Number of Providers	3.0
Average Number of Prescriptions PPPM*	3.5
Utilization of Intervention-Related Drugs**	
Average Number of Drugs***	1.4
Average Number of Claims	6.0
Average Days Supply	172.1
Average Amount Paid	\$375.27

\* Number of prescriptions per patient per month (PPPM) is the average for the 6 month baseline period

\*\* Based on 6 months of baseline claims data

\*\*\* A distinct drug is defined by using a coding system similar to the Hierarchical Ingredient Code List (HICL) in that distinct drugs are identified at the ingredient level.

### Increased Risk of ADE

The change in the number of patients identified as being at an increased risk of ADE is presented in Table 2. Overall, a reduction in the increased risk of ADE clinical indicators of 35.4% was achieved during the post-intervention period.

**Table 2: Changes in Risk of ADE**

Increased Risk of ADE	Target		
	Baseline	Jul-04	% Change
Peds OCD w/Fluoxetine, Fluvox or Sertraline	16	12	-25.0%
Peds w/Depression on Fluoxetine	47	23	-51.1%
Peds Off-label Use Antidepressants	1,175	765	-34.9%
Total	1,238	800	-35.4%



## BUSINESS ANALYSIS

The overall savings for the intervention is calculated in Table 3. Per patient per month (PPPM) drug amount paid for intervention-related drugs was calculated for the target group for the six-month baseline and six-month post-intervention periods. The post-period PPPM amount paid for the target group was subtracted from the baseline PPPM amount paid to obtain the estimated PPPM savings. The PPPM savings was then multiplied by the number of intervention months and number of target patients.

As a result of the intervention, the estimated per patient per month savings for intervention-related drugs was \$8.71. This yields an overall savings of \$64,701 for intervention-related drugs during the six-month post-intervention period.

**Table 3: Intervention-Related Drug Savings**

<b>Savings Calculation:</b>	
<b>Targeted Group: Actual Average Paid Amount Per Patient Per Month (Baseline)</b>	<b>\$62.77</b>
<b>Targeted Group: Actual Average Paid Amount Per Patient Per Month (Post)</b>	<b>\$54.06</b>
<b>% Change in Target Group from Baseline to Post</b>	<b>-13.88%</b>
<b>Estimated Savings Per Patient Per Month</b>	<b>\$8.71</b>
<b>Total Number of Targeted Patients</b>	<b>1,238</b>
<b>6-Month Total Savings</b>	<b>\$64,701.08</b>



## LIMITATIONS

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A control group was not utilized for this intervention. This limited the comparisons that could be performed in the analysis. Therefore, instead of being able to compare an intervention group with a non-intervention group, the analysis is essentially limited to changes in the intervention group before and after intervention.

The time frame of 6 months may not capture the full extent of the impact of the pediatric antidepressant intervention. Providers may be required some time before they can change their patient's drug regimens.

## CONCLUSIONS

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This pediatric antidepressant intervention focused on improving prescribing practices and reducing the overall cost of care. The intervention was successful in reducing the target patients flagged for increased risk of adverse drug events by 35.4%.

The amount paid for intervention-related drugs decreased \$8.71 in the post-intervention period. This yielded an overall savings of \$64,701 in intervention-related drug expenditures during the six-month post-intervention period.